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BEST PRACTICE & RESEARCH

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Fibrous dysplasia of bone

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Fibrous dysplasia of bone is a disease that can involve one or several bones and is characterized by bone deformities, pain and iterative fractures. Some patients can present with endocrine dysfunction (generally precocious puberty) and cutaneous café-au-lait spots. Some complications, such as nerve compression and malignant transformation, are uncommon. Many patients can, however, be asymptomatic. Diagnosis relies on X-ray examination and pathology. Prognosis is assessed by X-rays and markers of bone remodelling. Several breakthroughs in the understanding of the pathophysiology have been made in the past 10 years. It is now recognized that fibrous dysplasia is caused by a somatic activating mutation of the Gsα subunit of protein G, resulting in an increased cAMP concentration and thus in abnormalities of osteoblast differentiation, these osteoblasts producing abnormal bone. There is also an increase in interleukin-6-induced osteoclastic bone resorption, which is the rationale for treating these patients with bisphosphonates. In the past 10 years, the bisphosphonate pamidronate has been used by infusion for fibrous dysplasia (two courses per year), with good results with respect to pain and, in about 50% of patients, the refilling of osteolytic lesions.

Key words: fibrous dysplasia of bone; McCune–Albright syndrome; pamidronate; bisphosphonates; G-protein.

Fibrous dysplasia (FD) of bone is a rare congenital disease characterized by a focal proliferation of fibrous tissue in the bone marrow, leading to osteolytic lesions, deformities and fractures.[1] It may account for about 2.5% of bone disorders and 7% of so-called benign bone tumours.[2] The epidemiology of this disease is, however, not well known, and few studies have addressed the issue of treatment.

CLINICAL AND RADIOLOGICAL FEATURES

Many patients with FD are asymptomatic. The first symptoms often present during childhood or adolescence, but the diagnosis can be made in adults with mild or absent symptoms when an X-ray is performed for another reason. FD can be limited to a single bone (monostotic form) or may involve several bones (polyostotic form). In polyostotic FD, one side of the body is generally preferentially involved. Monostotic

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forms are often asymptomatic, and the diagnosis often comes to light as an incidental X-ray finding.[3]

Clinical symptoms

Pain

Patients with FD can suffer from bone pain, but this pain is seldom of articular origin, except when secondary osteoarthritis is present. Pain is often the consequence of an incomplete fracture, being either spontaneous or triggered by a minor trauma.[4] The intensity of the pain is variable, ranging from minimal to excruciating, and can be activated by palpation. This pain can have pseudo-inflammatory characteristics in some patients, with or without swelling.

Bone deformities

The shape of all long bones can be altered, giving a shepherd's crook deformity of the tibia or femur.[4] The forearm or the humerus can also be affected. When the craniofacial bones are involved[5], the most common presentation of the disease is facial asymmetry and swelling. These deformities can result in exophtalmy, abnormalities of tooth development and leontiasis ossea, and significant prejudice may arise as a result of the sufferer's appearance.

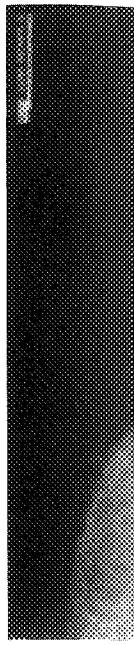
Fractures

A pathological fracture is the most common way of discovering FD.[3,4] Fractures of all the involved bones can occur, either because of deformities altering the mechanical properties of long bones during growth, or because of osteolytic lesions, which reduce cortical thickness. These fractures often result in severe functional incapacity, and corrective surgery is commonly required.

Radiological features

The radiological characteristics are diverse and depend on the degree of ossification of FD lesions, i.e. the proportion of bone and fibrous tissue in a lesion. The typical lesions appear to expand from the medulla to the cortex and are cystic (Figure 1). These lesions generally thin the surrounding cortical bone.[6] The cortex sometimes becomes sclerotic, especially after a previous fracture. The lesions usually exhibit a ground glass appearance or are radiolucent. Calcification may be visible if a significant amount of cartilage is present within the lesion. Sclerotic or mixed lesions can also be observed if there is a large amount of osseous tissue. All these types of lesion look benign, i.e. there is no periosteal reaction or soft tissue involvement.

The long bones are most commonly involved, and cystic lesions are usually observed. The ribs, iliac bones and small bones, for example those of fingers, can also display this type of lesion. Radiological diagnosis may be less easy for sites in the skull and facial bones because the lesions often resemble those of Paget's disease of bone or condensations. Spinal lesions are very rare and take many radiological forms, such as a lytic or pseudo-angiomatous appearance. In such cases, it is generally impossible to confirm the diagnosis only by imaging, and a bone biopsy is required.



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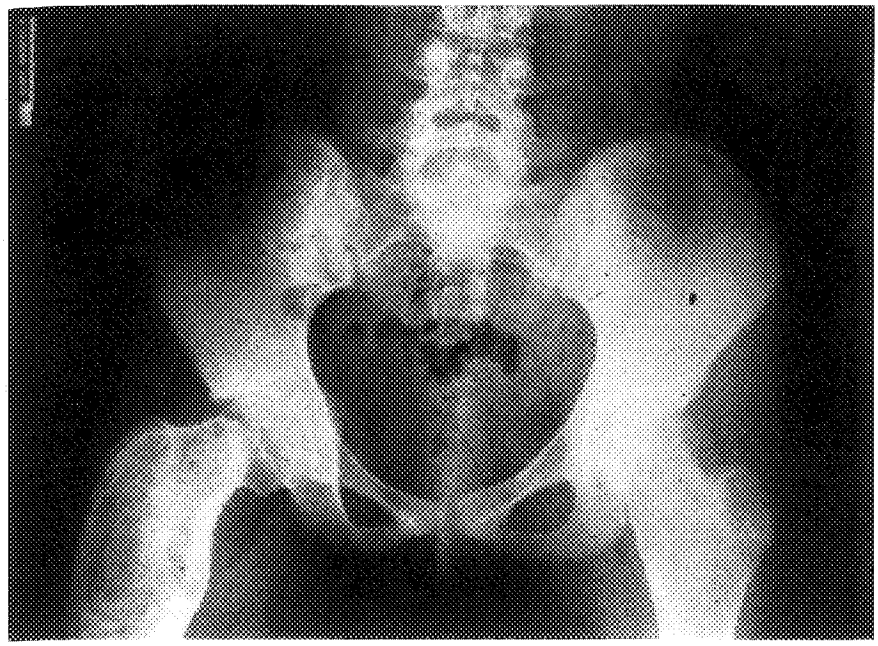

Figure 1. Typical X-ray appearance of fibrous dysplasia of bone involving both femoral necks in a 16-year-old girl.

McCune–Albright syndrome and other associations

McCune–Albright syndrome (MAS) was first described as a triad defined by the co-occurrence of precocious puberty, polyostotic FD and areas of brown hyperpigmentation of the skin (café-au-lait spots).[7,8] This hyperpigmentation is distinguished from that of neurofibromatosis by the shape of its borders, which are more irregular and similar to the coast of Maine, in contrast to those of neurofibromatosis, which are smoother, being more similar to the coast of California.[8] These café-au-lait spots are usually on the same side of the body as the bone involvement, often being arranged in a segmental pattern that follows the development lines of Blaschko.[9]

Multiple endocrine abnormalities may co-exist, for example thyroid nodules and hyperthyroidism[10], adrenal hyperplasia and hypercortisolism[11], pituitary tumours with acromegaly[10] or hyperprolactinaemia, and hypophosphataemic rickets and osteomalacia resulting from an inappropriately decreased reabsorption of phosphate from the renal tubules.[12] Non-endocrine abnormalities are occasionally present, affecting the liver, heart, thymus, spleen, liver, bone marrow, gastrointestinal tract and brain.[13] However, the vast majority of patients present with only two of the features of the triad and are still considered to have MAS.

The co-existence of FD and intramuscular myxomas may be seen in some patients (Mazabraud's syndrome), particularly those with polyostotic FD and MAS.[14] These myxomas are often large and multiple.

Diagnosis

The diagnosis should be based on the clinical, radiological and pathological findings. Clinical symptoms are non-specific, and the diagnosis has to be considered in patients with radiological features resembling those of FD. One should think of FD even in asymptomatic individuals. In polyostotic FD or in MAS, the radiological findings are often sufficient to provide a high probability of the diagnosis, and a bone biopsy is generally unnecessary. In contrast, many diagnoses are possible in monostotic FD, and a bone biopsy may be useful to confirm both the diagnosis of FD and that the lesion is not malignant. The bone biopsy is likely to result in a fracture, which can be difficult to heal. It should thus be avoided whenever possible, provided the radiological appearance allows differential diagnoses to be ruled out. Bone biopsy is usually performed in children during the surgical treatment of the first fracture. The most common differential diagnoses are Paget's disease of bone, cherubism, meningioma, angioma and osteofibrous dysplasia. In Paget's disease, dedifferentiation of the cortices is generally observed on X-ray, and there are no cystic cavities within the bone. In FD, cortical bone is thinned by the cancellous fibrous processes. The diagnosis of FD is also to be considered in a patient with numerous characteristic café-au-lait macules with or without precocious puberty.

Computed tomography (CT) and magnetic resonance imaging (MRI) can be of further assistance in studying bone abnormalities to prove the diagnosis of FD and avoid a bone biopsy. A ground glass appearance can be shown on CT scanning, as well as bone widening and islets of heterogeneous bone in the medulla.[15,16] Density values may vary, largely as a function of the amount of both fibrous and bone tissue. Density readings can be useful in distinguishing FD from other conditions such as osteomyelitis, Langerhans granulomatosis and some malignancies, in which bone density is significantly lower. In contrast, CT scans do not preclude the diagnosis of other cystic conditions. The fibrous tissue is responsible for the low-intensity signals seen on MRI T1-weighted and spin-echo sequences.[17] Variable-intensity signals, especially high-intensity signals in T2-weighted sequences, are a consequence of the heterogeneous histology seen in FD, and of metabolically active lesions.[18] Non-specific liquid intensity signals are encountered in cases of cystic FD lesions. High-intensity signals after gadolinium injection may be present, with no established cause.

When the diagnosis cannot be ascertained by imaging methods, bone biopsy is necessary, but the high risk of fracture of the involved bone needs to be considered. The most prominent histological characteristic[1] of FD is fibrous tissue made up of immature mesenchymal cells, expanding from the medullary cavity to the cortical bone. Long, spindle-shaped fibroblast-like cells are arranged in parallel arrays or whirls. They are embedded in a matrix of parallel collagen fibrils.[19] These spindle-shaped cells are abnormally differentiated to an osteoblastic phenotype as they express alkaline phosphatase. Spicules of woven bone are located in the fibrous tissue. These osteoblasts, involved in the deposition of lesional bone, produce a bone matrix enriched in some anti-adhesion molecules (versican and osteonectin) and poor in the pro-adhesive molecules osteopontin and bone sialoprotein.[20] Islands of hyaline cartilage can sometimes be noted embedded in the fibrous tissue.[19] Recently, three primary, but distinct, histological patterns have been described[21] – the Chinese writing, sclerotic/Pagetoid and sclerotic/hypercellular types – which seem to be characteristically associated with the axial/appendicular skeleton, cranial bones and gnathic bones respectively. The outer cortical bone is often invaded by FD as a consequence of the action of surrounding osteoclasts, resulting in cortical thinning[22] (Figure 2).

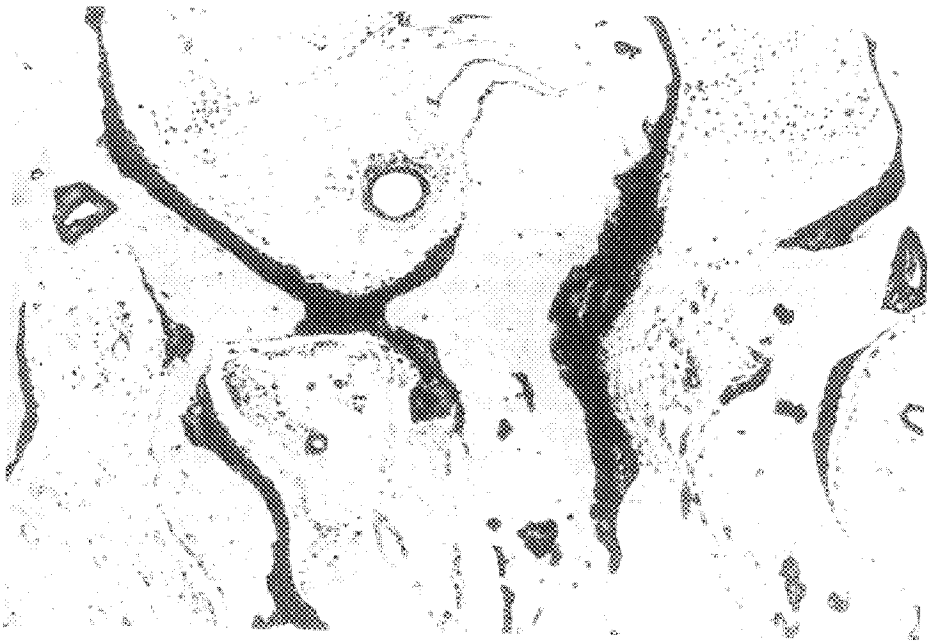

Figure 2. Histological aspect of fibrous dysplasia of bone (Goldner staining). Note the fibrous tissue in the bone marrow. Signs of osteomalacia are also present.

OUTCOME AND PROGNOSTIC INDICATORS

Prognosis

Usual evolution of FD

The general prognosis in FD is often good. Many patients have asymptomatic forms, and some severe childhood forms can be relieved in adults. Nevertheless, FD is also a severe disease in many patients, with highly significant disability resulting from pain, iterative fractures and deformity. Polyostotic forms seem to be more aggressive.[4] The prognosis also depends on the occurrence of complications.

Complications

Malignancies are rare in FD but can occur in both monostotic and polyostotic FD[23–26], their frequency varying from 0.5 to 4%. The most common malignancy seen is osteosarcoma, followed by fibrosarcoma and chondrosarcoma. The prognosis is poor. Around 50% of those patients suffering from a malignant transformation of FD have received radiotherapy, which appears to be the most important risk factor. The early recognition of a sarcoma in FD relies on the clinical history. Patients have rapidly developing symptoms such as pain and swelling. The characteristic finding on X-ray is the extension of the lesion through the cortex in soft tissues. When the diagnosis is suspected, CT and MRI are the best non-invasive techniques to suggest a provisional diagnosis of the malignant transformation of FD.[27]

Neurological complications occur as a result of nerve compression from the expansion of FD lesions. Exceptional consequences are blindness, deafness and spinal

cord compression. Urgent surgery may be required for optic nerve compression. When this highly specialized surgery has not immediately been available, high-dose corticosteroids (1 mg/kg per day) have been tried, with good results.

Assessment of prognosis

Evaluating the prognosis in patients with FD can be undertaken using biochemical markers of bone turnover and various imaging techniques, such as plain X-rays, CT, MRI and bone scanning. These techniques allow the clinician to study the severity of a lesion, its regional consequences and the number of possible other lesions.

Bone markers

Bone markers are used to assess the activity of the disease and the response to treatment. The classical markers in FD are serum total bone alkaline phosphatase (SAP) and urinary hydroxyproline (OHP). SAP is found to be elevated in about 75% of patients[8,28,29], its level being proportional to the extent and activity of the disease. The same is true for OHP, although it is less sensitive as a marker. In any one patient, SAP activity can vary over time, according to the spontaneous activity of the disease.[28] Osteocalcin (OC), urinary deoxypyridinoline (D-Pyr) and the C-telopeptide of type I collagen breakdown products (CTX) can also be raised in patients with FD.[30] However, OC and urinary D-Pyr have been used in only a small number of patients, so it is difficult to draw a firm conclusion with regard to their sensitivity in assessing the activity of FD and the response to treatment. In contrast, urinary CTX levels are increased in active forms of FD, showing a sharp decrease after treatment with the bisphosphonate pamidronate.[31,32]

Imaging

It is important to perform a bone scan at least once, when the diagnosis is made, in order to map the sites of disease. There is an increased uptake in dysplastic lesions, generally with a lower intensity than is seen in Paget's disease. CT scanning is often necessary to assess the risk of fracture as it reveals fissures or thinning of cortices that can be missed on plain X-rays. MRI is less useful as the clinical relevance of the altered signals is unclear. MRI may sometimes reveal features of the exceptional malignant transformation.

Bone densitometry

It has recently been suggested that hip densitometry could be helpful in assessing the response to bisphosphonate treatment, revealing a sharp increase in the bone mineral density of femoral neck lesions after only 1–2 years of treatment.[33,34]

NEW UNDERSTANDINGS

In pathophysiology

Mutations of the Gsα subunit gene that lead to the constitutive activation of protein Gs and cAMP production have been identified in various tissues taken from MAS patients.[35,36] These mutations involve a substitution of arg at position 201 by his or cys,

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which can be detected in varying amounts. It has been suggested that the severity of the disease is proportional to the abundance of the mutation.[37] In each tissue, the mutated gene co-exists with the normal gene as a mosaic, and the presence of normal cells is compulsory for the viability of the mutated cells.[38] These mutations are found in all hyperplastic or adenomatous endocrine tissues, in café-au-lait spots[39], in non-endocrine tissues and in bone[40,41], while other tissues are normal. In isolated FD of bone, the dysplastic process is highly likely to result from the same somatic mutation as in MAS, but at a later time in development, resulting in a limited distribution of the mutant cells.[41]

The cells present in FD are poorly differentiated osteoblasts with an increased proliferation rate, but they express markers of osteoblastic differentiation such as alkaline phosphatase and OC. In these cells, regulation of normal differentiation is disrupted.

Some genes downstream in the signalling cascade may be affected by the elevation of cAMP caused by the activation of Gsα protein in osteoprogenitor cells. Gsα protein increases the expression of *c-fos*[42] and other oncogenes through the activation of cAMP-dependent protein kinase (PKA). The increased expression of the product of *c-fos*, Fos, seems to be localized to the osteoblastic precursors. The catalytic subunits of PKA translocate to the nucleus and phosphorylate cAMP-responsive transcription factors such as cAMP response element binding protein (CREB) and the related CREM proteins. The transcription of *c-fos* is then activated, Fos binding with Jun to form a heterodimer named AP-1. AP-1 complexes are highly expressed in the proliferative phase of osteoblast development and can suppress the expression of late markers of osteoblastic differentiation, such as OC. The consequence of the overexpression of Fos in transgenic mice is an abnormal bone remodelling and bone lesions reminiscent of FD.[43] It has been suggested that the increased cAMP level could downregulate another factor involved in osteoblast differentiation, CBFA-1, thus contributing to the pattern of abnormal differentiation.[44]

In abnormally differentiated osteoblasts in FD lesions, the secretion of interleukin (IL)-6 appears to be increased as a result of Gs activation, by a cAMP-dependent mechanism[45], with a consequential activation of the surrounding osteoclasts, thus permitting the FD lesion to expand. The beta-chain of platelet-derived-growth-factor (PDGF-B) has been shown to be increased in FD and could be important for osteoclast activation. The level of sex steroid receptors in FD osteoblasts is elevated and could account for the increased aggressiveness of FD during puberty, pregnancy or the use of oral contraceptives.[46,47]

These biological points are summarized in Figure 3.

In treatment

So far, the only treatment for FD has been orthopaedic surgery, consisting of preventive measures (curettage, bone grafting and the internal fixation of long bones) and the management of fractures. Calcitonin, mithramycin and etidronate have been tried in a few cases, with poor results. Spontaneous improvement has never been observed. No randomized controlled trial has been undertaken to study these treatments.

What is new, however, is the use of a second-generation bisphosphonate, pamidronate, to treat the increased osteoclastic resorption of FD, as in Paget's disease. The first patients were treated 10 years ago in our department, and several sets of results have been published concerning the first 9, 20 and 28 patients.[30–32] Adult patients receive

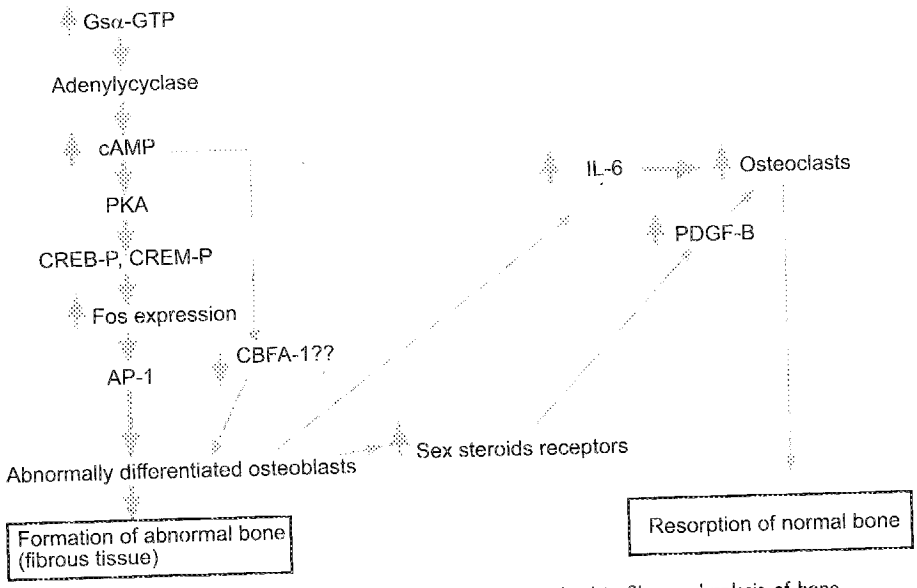

Figure 3. Possible pathophysiological mechanisms involved in fibrous dysplasia of bone.

180 mg intravenous pamidronate (60 mg per day for 3 days) every 6 months for a minimum of 2 years. After that, they are often treated once a year, according to their response to the treatment. Patients receive a daily supplementation with calcium (1 g per day) and vitamin D (800 IU per day) in order to avoid secondary hyperparathyroidism. The effects of intravenous pamidronate have been assessed in several ways: in clinics, biologically and using X-rays. Intravenous pamidronate markedly decreases bone pain without the early development of drug resistance. When patients with a relapse of pain were re-treated, a new positive response was obtained in all but one patient (who had been treated for 8 years with good results at the time when resistance to treatment developed).

Bone remodelling is significantly reduced, as shown by markers of bone remodelling (alkaline phosphatase and CTX). A trend towards secondary hyperparathyroidism has been observed in the first patients, showing that the use of calcium and vitamin D supplementation should be checked.

A refilling of osteolytic areas with cortical thickening has been observed in about 50% of treated patients (Figures 4 and 5). This effect is sometimes striking, and at least 18 months are needed to observe it. No predictive factor for the radiographic response (for example, sex, age, bone markers or number of sites) has been found. These findings suggest an increase in bone strength, with perhaps a decrease in the risk of fracture. Absorptiometry has confirmed these findings by a rapid and significant increase in bone mineral density at the involved sites.[33,34] Two other bisphosphonates have been tried in fewer than 10 patients: olpadronate (S Papapoulos, personal communication, 1998) and alendronate in a woman with McCune–Albright syndrome[33], with very good results.

Children or adolescents can also be treated, but intravenous pamidronate must be used cautiously during growth. These patients can receive 1 mg/kg per day over 3 days in every 6 months. The improvement is similar to that seen in adults. It may be more

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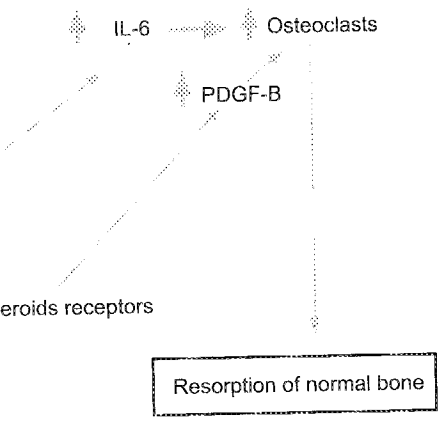

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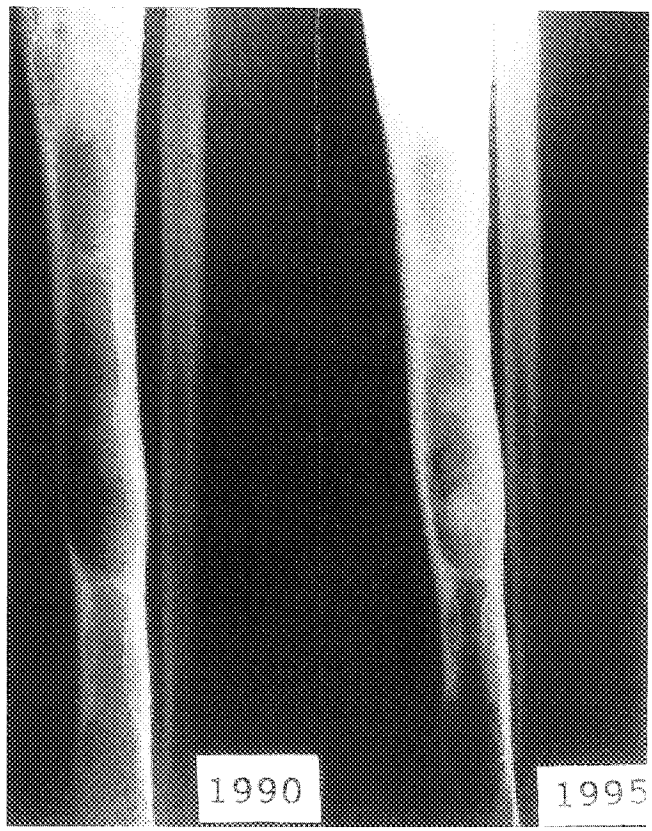

Figure 4. Radiological appearance of a tibia before and after 5 years of treatment with intravenous pamidronate.

efficacious to treat young patients to limit the worsening of lesions, thus decreasing the subsequent fracture risk.

Treatment with intravenous pamidronate is well tolerated, as in malignant osteopathies and Paget's disease. Transient fever or an increase in bone pain may be noticed. Three cases of localized mineralization defect have been observed, one of them involving a 13-year-old boy[30] with hypophosphataemia, which probably contributed to his mineralization defect. In these three patients, it was possible to resume further courses of pamidronate without any problem.

Only open studies have been published. Nevertheless, bone lesions are highly heterogeneous, and thus assessment criteria are very difficult to standardize. In addition, FD is a rare disease. Therefore, it does not currently seem to be possible to carry out a randomized trial. Furthermore, no spontaneous improvement has been described.

MANAGEMENT OF FD

To confirm the diagnosis

Making the diagnosis of FD is often easy for patients with polyostotic FD or MAS. Radiological criteria are generally sufficient, and the use of bone biopsy is exceptional.

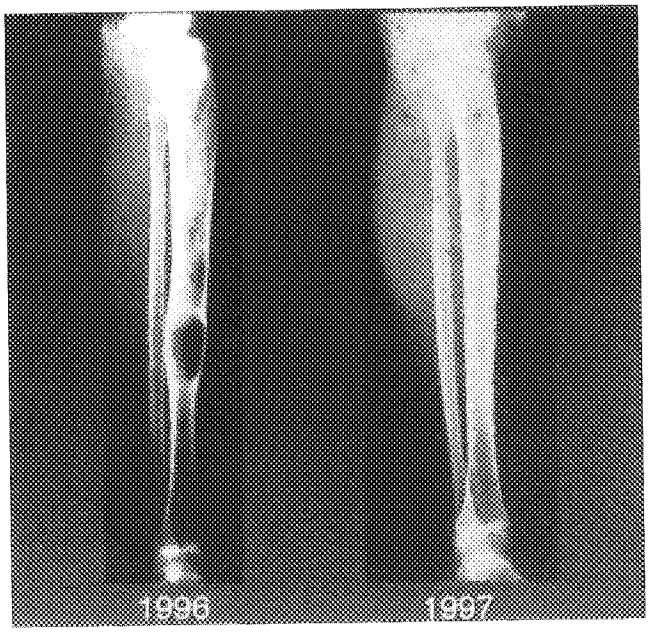

Figure 5. X-ray of a tibia before and after 18 months of treatment with intravenous pamidronate in a 16-year-old boy.

For patients with monostotic FD, the diagnosis of several bone tumours can be evoked. Thus, the history, clinical symptoms, and biochemical and radiological features have to be carefully studied to reach a diagnosis. When the diagnosis is dubious, a bone biopsy is indicated, providing it is not too risky.

To look for other sites

Bone scanning is necessary to discover all the sites of FD in an individual. X-rays of all the involved sites have to be taken.

To establish prognosis

FD is commonly asymptomatic, diagnosis being made from X-rays requested for another reason. Is it then worth treating all patients, or is it better to treat only patients with complications of the disease (pain, deformation, fractures or nerve compression)? In our opinion, it seems reasonable to treat not only symptomatic FD, but also sites at risk of complications, i.e. when there is a clear risk of fracture (for example, a femoral lytic lesion), when there is a high risk of nerve compression (craniofacial sites) and when the occurrence of secondary osteoarthritis is possible (osteoarthritis of the hip secondary to FD of the femur), as in Paget's disease. There is no randomized controlled trial studying this aspect.

Medical treatment in practice

Patients usually receive a course of 180 mg intravenous pamidronate over 3 days every 6 months. It is recommended that this treatment be continued for at least 2 years.

Later on, courses can be delivered once a year. Patients should also receive calcium and vitamin D supplements. Hypophosphataemia must be corrected in MAS patients in order to avoid osteomalacia.

Orthopaedic treatment

Patients presenting with fractures generally require surgery. Internal fixation is generally performed, and cortical bone grafts are sometimes used to fill important bone defects. Cancellous bone grafts, which are prone to resorption by the dysplastic process, are not recommended. Preventative surgical measures are necessary when the risk of fracture is very high, for example in a large lytic lesion occupying the femoral neck.

SUMMARY

Clinical key points

FD of bone is a disease underlying bone deformities, pain and fractures. Many patients can, however, be asymptomatic. FD can be monostotic (involving one bone) or polyostotic (involving several bones), some patients presenting with endocrine dysfunction (usually precocious puberty) and cutaneous hyperpigmentation (café-au-lait spots). Some complications, for example nerve compression and malignant transformation, are exceptional.

Key points in diagnosis

Diagnosis relies on X-ray examination and sometimes on pathology, but bone biopsy should be avoided whenever possible because of the risk of iatrogenic fracture. Prognosis is assessed by X-rays and markers of bone remodelling, and CT scanning can be used to assess the risk of fracture.

Pathophysiological key points

The understanding of the pathophysiology of FD has been significantly improved in the past 10 years. It is now recognized that FD is caused by a somatic activating mutation of the Gsα subunit, resulting in osteoblast differentiation abnormalities arising from an increase in cAMP concentration. These osteoblasts produce abnormal fibrous and woven bone. There is also an IL-6-induced increased osteoclastic bone resorption, which is the rationale for treating these patients with potent anti-resorptive agents such as bisphosphonates.

Key points in treatment

In the past 10 years, the bisphosphonate pamidronate has been used in FD, with good results in terms of pain and, in about 50% of patients, the refilling of osteolytic lesions. This treatment is well tolerated.

Practice points

- clinical features of FD are pain, which is sometimes pseudo-inflammatory, bone deformities and fractures
- the radiological characteristics of FD are diverse and depend on the proportion of bone and fibrous tissue in a lesion. Typical lesions appear to extend from the medulla to the cortex and are fibrous or cystic in nature. These lesions generally thin the surrounding cortical bone
- prognosis in patients with FD can be evaluated using biochemical markers of bone turnover and various imaging techniques, such as plain X-rays, CT, MRI and bone scanning. These techniques allow the clinician to study the severity of a lesion, its regional consequences and the number of other possible lesions
- the different steps of practical management are:
  - confirming the diagnosis
  - searching for other sites
  - establishing the prognosis
  - prescribing medical treatment when it is necessary

Research agenda

- discovery of the aetiology of the somatic mutations causing FD may allow prevention during pregnancy
- a further understanding of the abnormalities occurring in the differentiation of osteoblasts is necessary in order to improve the treatment of FD
- studies aimed at determining the optimal regimen of bisphosphonates are needed; these should be randomized controlled trials

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re diverse and depend on the proportion
Typical lesions appear to extend from the
or cystic in nature. These lesions generally

evaluated using biochemical markers of
echniques, such as plain X-rays, CT, MRI
allow the clinician to study the severity of
d the number of other possible lesions

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